

Clinical frailty is independently associated with non-prescription of anticoagulation in older patients with atrial fibrillation

Short title: Frailty in Atrial Fibrillation

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Abstract

Aim

Anticoagulation is underused in older patients with atrial fibrillation (AF). Scoring systems such as CHA₂DS₂-VASc and HAS-BLED are recommended to guide clinicians in anticoagulation decisions, but patients' frailty may be an under-recognized factor. We investigated the association between the Clinical Frailty Scale (CFS) and community anticoagulation prescribing habits in patients aged over 75 years with AF admitted acutely to hospital.

Methods

Data was gathered retrospectively over 3 months on individuals admitted under a medical team to a tertiary teaching hospital in the United Kingdom. Demographics, AF history, CHA₂DS₂-VASc, HAS-BLED and CFS were collected. Bivariable analysis compared anticoagulated and non-anticoagulated groups. Each component of the CHA₂DS₂-VASc and HAS-BLED scores, as well as frailty, age and gender were entered in a multivariable analysis.

Results

419 patients with known AF were included. 215 were not anticoagulated (51.3%) on admission. Non-anticoagulated individuals were older (median age 87 (interquartile range (IQR) 7) vs 83 years (IQR 6), $p<0.001$), more likely to be frail (81.4% vs 52.5%, $p<0.001$) and had lower CHA₂DS₂-VASc scores (median 4 (IQR 2) vs 5 (IQR 2), $p=0.01$). In the multivariable analysis frailty had the strongest effect against anticoagulation prescription (OR:0.77 95%CI 0.70-0.85, $p<0.001$) compared to other significant risk factors like age (OR:0.98 95%CI 0.97-0.98, $p<0.001$) and bleeding risk (OR:0.85 95%CI 0.74-0.97, $p=0.02$).

Conclusions

Frailty is associated with non-prescription of anticoagulation, independently of CHA₂DS₂-VASc and HAS-BLED. It may be an important unmeasured factor in anticoagulation decisions. The utility of explicit frailty measurements in anticoagulation decisions and patient outcomes needs researching.

Keywords

Anticoagulation

Atrial Fibrillation

Frailty

Pharmacology

Stroke

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in older people and its prevalence increases with age.^{1,2} It is a risk factor for ischaemic stroke and is a powerful predictor of disability, dementia and death due to the increased severity of cardioembolic strokes compared to other stroke aetiologies.² Cardioembolic strokes constitute a disproportionate burden of the total cost of stroke, with a 2-fold increase in median total healthcare costs compared to non-AF stroke.³ As the population becomes older, the number of individuals with AF is set to increase with cardioembolic stroke imposing a greater burden on patients, families and healthcare resources.^{1,4}

Anticoagulation is the only licensed medication to reduce the risk of stroke⁵ but due to the perceived increased risk of complications^{6,7} lower rates of anticoagulation use is seen, especially in older patients, with up to half not being anticoagulated.^{8,9}

Frailty is defined as a state of vulnerability to adverse outcomes from stressors⁷ and it is recognised that frail individuals may be more susceptible to medication side effects,¹⁰ including those from anticoagulation. Clinical trials rarely include frail patients, therefore, deciding who would benefit from anticoagulation can be challenging. Despite risk scores such as CHA₂DS₂-VASc¹¹ [which assigns 1 point where there is a history of congestive cardiac failure, hypertension, diabetes mellitus, vascular disease, age ≥65 years and female gender, and 2 points if age ≥75 years or there is a history of prior stroke/ transient ischaemic attack (TIA)] and HAS-BLED¹² [which assigns 1 point to uncontrolled hypertension >160mmHg systolic, abnormal renal or liver function, labile international normalised ratio (INR), age >65, use of antiplatelet/anticoagulation which may increase risk of bleeding and alcohol use defined as >8 drinks/week] guiding clinicians when weighing up the risk of stroke against the risk of bleeding¹³, guidelines do not provide specific advice on anticoagulation decisions for frail older people who are more susceptible to adverse outcomes.^{14,15}

Our study investigated the association between clinical frailty as measured by the 9-point Clinical Frailty Scale (CFS)¹⁶ (Figure 1) and community anticoagulation prescribing habits in patients aged 75 years and over, admitted acutely to hospital. An understanding of the relationship between clinical frailty and community prescribing of anticoagulants, independently of recognised decision aid tools such as CHA₂DS₂-VASc and HAS-BLED, may help elucidate the importance of the frailty syndrome in AF, as well as aiding the development of future clinical decision-making tools that are more appropriate for this vulnerable population.

Method

Data collection

We conducted a retrospective observational study in a 1,000-bed teaching hospital in England, between 1st January and 31st March 2014. Inclusion criteria were age ≥ 75 years, admission under a general medical team, a history of AF, and a frailty score documented on admission. In our centre, the CFS is routinely collected in all non-elective admissions aged 75 years or more.¹⁷

The CFS aims to capture the pre-admission, or baseline, frailty status and is calculated within 72-hours of admission by a clinician and recorded in the patient medical records. Patients were divided into two groups: 'non-frail' (CFS scores 1-4) and 'frail' (CFS scores 5-8). Data including patient age, sex, admission and discharge diagnosis, anticoagulation status, CHA₂DS₂-VASc, HAS-BLED and frailty scores were retrospectively collected from discharge letters.

This study was part of a Service Evaluation Audit registered with our center's Safety and Quality Support Department (project register number 3962). Formal confirmation was received that approval from the ethics committee was not required.

Statistical analysis

Data was analyzed using R (version 3.1.2). A p value <0.05 was considered statistically significant throughout data analysis. Initially bivariable comparisons for continuous data between anticoagulated and non-anticoagulated groups were tested for normality using Shapiro-Wilk testing, with subsequent analysis using the Student's t-test or Mann-Whitney U-test for parametric and non-parametric data respectively. Categorical data was analysed between cohorts using the chi-squared test. The multivariable logistic regression analysis included the following predictors of anticoagulation prescription: frailty, age, gender and the individual components of the CHA₂DS₂-VASc and HAS-BLED scores, rather than the cumulative scores, to avoid duplication. Due to the overlap in hypertension which has different definitions between the two scoring systems, we included hypertension as per the CHA₂DS₂-VASc score in the multivariable analysis.

Results

419 patients with known AF were included in the study. 215 were not anticoagulated (51.3%) on admission and 204 (48.7%) were anticoagulated. The use of warfarin (94.1%) heavily outnumbered both dalteparin (0.9%) and direct oral anticoagulants (DOACs) - dabigatran 4.1%; rivaroxaban 0.9%, apixaban 0%. In the frail cohort, 6 individuals were on DOACs compared to 5 in the non-frail group. The non-anticoagulated group were older (median age 87 years (interquartile range {IQR: Q₃-Q₁} 7) vs. 83 years (IQR 6), p<0.001) and had a higher prevalence of frailty (81.4% vs 52.5%, p <0.001). Individuals not admitted on anticoagulation had lower CHA₂DS₂-VASc scores (median 4 (IQR 2) vs. 5 (IQR 2), p=0.01) compared to the anticoagulated group but there were no significant differences in HAS-BLED scores between the two groups (p=0.07) (Table 1).

As clinical frailty increases, there are fewer anticoagulated individuals per CFS. (Figure 2) For example, at CFS 3 and 4, between 70-73% are on anticoagulation compared to CFS 7 and 8, where the proportion of anticoagulated individuals has dropped to 29% and 7%, respectively. However, the same pattern is not seen with changes in the CHA₂DS₂-VASc or HAS-BLED scores. Our results show that having

had a previous stroke or TIA meant that individuals were more likely to be on anticoagulation ($p=0.01$) and a history of prior bleeding or predisposition to bleeding meant that individuals were significantly less likely to be anticoagulated ($p=0.001$). The presence of other risk factors for stroke or bleeding as per the components of CHA₂DS₂-VASc and HAS-BLED scores did not differ between anticoagulated and non-anticoagulated groups (all $p>0.05$) (Table 1).

Multivariable analysis of frailty, age and gender along with the components of the CHA₂DS₂-VASc and HAS-BLED scores showed that individuals are more likely not to be on anticoagulation at admission, if they are older, frailer and are felt to be at risk of bleeding. However, having had a previous stroke or TIA, or having a history of congestive cardiac failure were associated with being prescribed anticoagulation. (Table 2)

Frailty was the strongest independent predictor of not being on anticoagulation at admission compared to age and bleeding risk (OR:0.77 95%CI 0.70-0.85, $p<0.001$), emphasizing that frail individuals are 23% less likely to be anticoagulated on admission to hospital.

Discussion

Our study explored the association between clinical frailty and community anticoagulation prescription habits in patients aged over 75 years admitted acutely to hospital. Nearly half the patients aged over 75 years in our study were not on anticoagulation, with frailty, age and bleeding risk emerging as independent predictors of non-anticoagulation. Multivariable analysis suggested that frailty was the strongest predictor for not being on anticoagulation at admission even more so than bleeding risk. This indicates that despite explicit frailty measurements not being routinely conducted in the community, a clinical impression of an individual as being frail is negatively associated with anticoagulation prescription.

Our results highlight the important role frailty plays anticoagulation decisions, and the low rates of anticoagulation observed in this study highlight that making such decisions in frail older individuals is challenging. Previous studies report that clinician reluctance to prescribe anticoagulation, because of the difficulty in choosing between stroke and bleeding risk, is a major reason for under-treatment¹⁸⁻²⁰, suggesting that more help and guidance is needed. However, specific geriatric characteristics that would allow safer prescription of anticoagulation have not been determined and existing guidelines are drawn from results of those with greater physiological reserve and as such are less likely to suffer adverse outcomes.¹⁰

This highlights the need for safer and more reliable methods of assessing the risks and benefits of anticoagulation in frail individuals, including a greater understanding of the implications of frailty in such decisions. In large epidemiological studies, the frailty phenotype has been validated as a predictor of short and long-term adverse outcomes, including death^{21,22} and the CFS has been shown to have accuracy in predicting in-hospital adverse outcomes.¹⁷ Because frail individuals develop numerous deficits across multiple domains of disease, relying on rigid scoring systems such as CHA₂DS₂-VASc and HAS-BLED, which contain overlapping risk factors for both stroke risk and bleeding risk, may be less applicable in frail cohorts.

Our study has some limitations. Being a single-site study with a relatively small sample size of individuals admitted acutely to hospital, the individuals in the study may not be representative of the broader population. By nature of being a retrospective study, data collection may be limited by the record keeping, though the effects of this are limited by excluding patients without discharge summaries or recorded frailty scores, which includes those who died in hospital.

Safer and more reliable methods of assessing the risks and benefits of anticoagulation in the frail older population would be useful in clinical practice. Frailty scores are not routinely measured in primary or secondary care, yet they may offer more flexibility and judgement to the clinician to make personalised,

holistic decisions. In our study, increasing clinical frailty was associated with a lower proportion of individuals on anticoagulation, which suggests that clinicians already have an inherent idea of the concept of frailty and increased adverse outcomes. This is further supported by previous studies that show measured frailty scales correlate well with a clinician's initial global assessment of frailty.²³ Because of the complexity of treatment in the older population, we propose that additional information gained from explicit frailty measurements may translate into clearer decision-making about anticoagulation. Further work is required to determine whether such assessments of frailty, and their role in determining anticoagulant prescribing, affects clinical outcomes.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Figure1

Each patient admitted to hospital over >75 years have their clinical frailty calculated on admission as per the 9-point Clinical Frailty Scale.

Available from: [http://geriatricresearch.medicine.dal.ca/pdf/Clinical Frailty Scale.pdf](http://geriatricresearch.medicine.dal.ca/pdf/Clinical%20Frailty%20Scale.pdf)



Figure 2

The number and proportion of individuals not anticoagulated (black) compared to anticoagulated (white), when separated by clinical frailty scale, CHA₂DS₂-VASc and HAS-BLED scores.

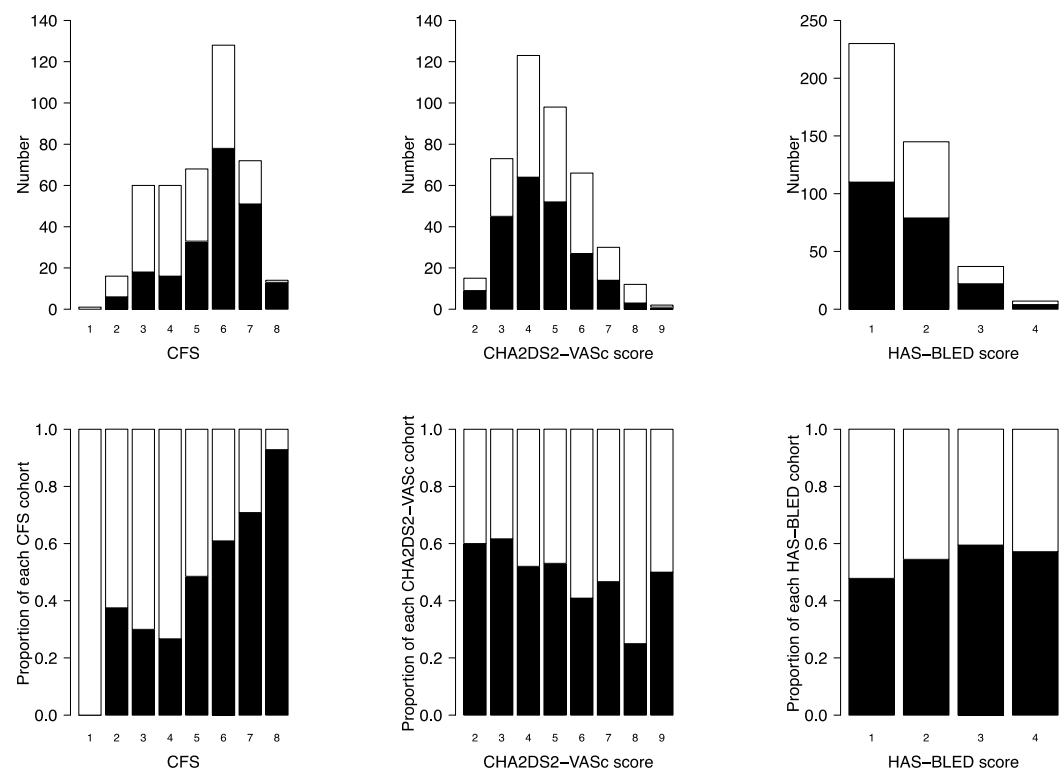


Table 1. Patient demographics data and bivariable analysis for significance between not-anticoagulated and anticoagulated groups.

	Not anticoagulated 215	Anticoagulated 204	Significance
Frail	175 (81.4%)	107 (52.5%)	p<0.001
Median Age	87 (IQR 7)	83 (IQR 6)	p<0.001
Male	93 (43.3%)	96 (47.1%)	<i>p=0.43</i>
Median CHA₂DS₂-VASc	4 (IQR 2)	5 (IQR 2)	p=0.01
Congestive cardiac failure	58 (27.0%)	65 (31.9%)	<i>p=0.27</i>
Hypertension	146 (67.9%)	147 (72.1%)	<i>p=0.35</i>
Diabetes	45 (20.9%)	48 (23.5%)	<i>p=0.52</i>
Stroke/Transient ischemic attack	56 (26.0%)	77 (37.7%)	p=0.01
Vascular disease	49 (22.8%)	55 (27.0%)	<i>p=0.32</i>
Median HAS-BLED	1 (IQR 1)	1 (IQR 1)	<i>p=0.07</i>
Liver abnormalities*	1 (0.005%)	2 (0.01%)	<i>p=0.53</i>
Renal abnormalities**	12 (0.06%)	14 (0.07%)	<i>p=0.59</i>
Prior bleeding or predisposition	37 (0.17%)	14 (0.07%)	p=0.001
Labile INR***	2 (0.009%)	6 (0.03%)	<i>p=0.13</i>
Alcohol >8 drinks/week	1 (0.005%)	3 (0.01%)	<i>p=0.29</i>
Medication with bleeding risk****	5 (0.02%)	3 (0.01%)	<i>p=0.52</i>

As per the HAS-BLED scoring criteria: *cirrhosis or Bilirubin >2x Normal or AST/ALT/ALP >3x Normal, ** Dialysis dependent, previous transplant, creatinine >2.26 mg/dL or >200 µmol/L, *** Unstable/high International Normalized Ratio (INR), Time in Therapeutic Range <60%, **** Antiplatelet agent/ NSAID use

Table 2. Multivariable analysis of odds ratios for anticoagulation

	Odds ratio for anticoagulation (95% CI)	Significance
Frail	0.77 (0.70-0.85)	p<0.001
Age	0.98 (0.97-0.98)	p<0.001
Male	0.98 (0.89-1.06)	<i>p=0.59</i>
CHA₂DS₂-VASc		
Congestive cardiac failure	1.12 (1.02-1.24)	p=0.02
Hypertension	1.05 (0.95-1.15)	<i>p=0.37</i>
Diabetes	0.94 (0.84-1.04)	<i>p=0.24</i>
Stroke/Transient ischemic attack	1.19 (1.09-1.31)	p<0.001
Vascular disease	1.04 (0.94-1.14)	<i>p=0.51</i>
HAS-BLED		
Liver abnormalities*	0.91 (0.53-1.55)	<i>p=0.72</i>
Renal abnormalities**	1.06 (0.88-1.26)	<i>p=0.55</i>
Prior bleeding or predisposition	0.85 (0.74-0.97)	p=0.02
Labile INR***	1.34 (0.98-1.84)	<i>p=0.07</i>
Alcohol	1.45 (0.92-2.30)	<i>p=0.11</i>
Medication with bleeding risk****	0.80 (0.58-1.10)	<i>p=0.17</i>

As per the HAS-BLED scoring criteria: *cirrhosis or Bilirubin >2x Normal or AST/ALT/ALP >3x Normal, ** Dialysis dependent, previous transplant, creatinine >2.26 mg/dL or >200 µmol/L, *** Unstable/high International Normalized Ratio (INR), Time in Therapeutic Range <60%, **** Antiplatelet agent/ NSAID use